OxyContin
C.R.Tablets
NDA #20-553
Final Study Report
OC92-1001
February 20, 1997
Volume 1 of 5

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Purdue Pharma L.P.

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IND/NDA

February 20, 1997

SUBMITTED IN DUPLICATE
SUPPLEMENTAL APPLICATION
FINAL POSTMARKETING STUDY REPORT

Curtis Wright, M.D.
Anesthetic/Critical Care & Addiction Drug Products
Office of Drug Evaluation 3
Food and Drug Administration
HFD-170, Document Control Room 9B23
5600 Fishers Lane
Rockville, MD 20857

RE: **OXYCONTIN® (oxycodone hydrochloride)**
NDA #20-553

Dear Dr. Wright,

Please refer to our New Drug Application, NDA #20-553, for OxyContin® 10, 20 and 40 mg Tablets filed December 28, 1994 (approved December 12, 1995) which included the study protocol only for Study No. OC92-1001. Attached hereto, please find the hard copy Final Study Report.

The primary objectives of this study were to "compare the peak-to-trough fluctuation and the trough variation in steady-state plasma oxycodone and morphine concentrations."

It was concluded that "While CR oxycodone was comparable with CR morphine in efficacy, there were differences in clinical pharmacokinetics that favored CR oxycodone. Similarly, the safety profiles of CR oxycodone and CR morphine were similar, but small differences suggested CR oxycodone may have benefits over CR morphine in individual patients. Overall, this study provides definitive evidence of the clinical equivalence of CR oxycodone and CR morphine in controlling cancer pain."

If you have any questions or require additional information, please contact me at the number below.

Sincerely,

Beth Kennedy
Associate
Drug Regulatory Affairs & Compliance
(203) 854-7289

STUDY REPORT

OxyContin™ Tablets

PROTOCOL NO. OC92-1001

Double-blind, randomized, q12h multiple-dose, parallel-group comparison of the pharmacokinetic and pharmacodynamic profiles of controlled-release oxycodone (OxyContin™) and MS Contin® tablets in patients with chronic cancer-related pain

Investigators:

Barry S. Berman, MD
(previous principal investigator,
Michael S. Roberts, M.D.; #1557 and 1311)

Marc L. Citron, MD (#711)

Ronald Kaplan, MD (#1196)

Patricia Mucci-LoRusso, DO (#1537)

Michael R. Mullane, MD (#1510)

Winston C.V. Parris, MD, FACPM (#716)

Susan Rabinowe, MD
(previous principal investigator,
William A. Ferri, Jr., MD; #1539)

Peter T. Silberstein, MD (#1488)

Sharon M. Weinstein, MD (#1538)

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The Purdue Frederick Company
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Yonkers, NY 10701

STUDY DATES:

START DATE: June 1, 1994

END DATE: December 27, 1995

REPORT DATE: September 27, 1996

IND. NO. 29,038

FINAL: September 27, 1996

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25 September 1996
Date

Paul D. Goldenheim, M.D.
Vice President

9-27-96
Date

REVISIONS

Revision No.	Revision Date	Revision Approval - P. Goldenheim, M.D.
1		
2		
3		
4		

DOUBLE-BLIND, RANDOMIZED, Q12H MULTIPLE-DOSE, PARALLEL-GROUP COMPARISON OF THE PHARMACOKINETIC AND PHARMACODYNAMIC PROFILES OF CONTROLLED-RELEASE OXYCODONE (OXYCONTIN™) AND MS CONTIN® TABLETS IN PATIENTS WITH CHRONIC CANCER-RELATED PAIN

SUMMARY

I. TITLE: Double-blind, randomized, q12h multiple-dose, parallel-group comparison of the pharmacokinetic and pharmacodynamic profiles of controlled-release oxycodone (OxyContin™) and MS Contin® tablets in patients with chronic cancer-related pain

II. INVESTIGATORS

Barry S. Berman, MD (previous principal investigator, Michael S. Roberts, MD; #1557 and 1311)
Marc L. Citron, MD (#711)
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Peter T. Silberstein, MD (#1488)
Sharon M. Weinstein, MD (#1538)

III. TRIAL DATES: June 1, 1994 to December 27, 1995

IV. OBJECTIVES/STUDY DESIGN: This double-blind, parallel-group study compared the steady-state pharmacokinetic and pharmacodynamic profiles of controlled-release (CR) oxycodone (OxyContin™) and CR morphine (MS Contin®) given q12h in patients with chronic cancer-related pain. The primary objectives were to compare the peak-to-trough fluctuation and the trough variation in steady-state plasma oxycodone and morphine concentrations.

Patients were randomly assigned to treatment with CR oxycodone or CR morphine tablets q12h for 3-12 days. The dose of q12h medication was titrated until pain control was acceptable to the patient and any adverse experiences were tolerable. Rescue medication was allowed. Pharmacokinetic and pharmacodynamic procedures were performed after stable pain control had been maintained for at least 48 hours, at 0 hours and 3 hours after the 8:00 AM dose of study medication. Patients who could not be stabilized within 10 days were discontinued. A total of 80 evaluable patients was planned. Nine sites participated in the study.

V. STUDY POPULATION/EVALUABILITY GROUPS/PATIENT DISPOSITION: Patients who required treatment with opioid analgesics for chronic, cancer-related pain were enrolled. After the study was completed and before the treatment code was unblinded, the following three evaluability groups were defined for the statistical analysis:

- Intent-to-treat population: patients who received at least one dose of study medication,
- Pharmacokinetic-pharmacodynamic population: patients who had at least one phlebotomy for plasma opioid concentration determination and a simultaneous pharmacodynamic determination, and
- C_{max}/C_{min} population: patients who had plasma opioid concentration determinations at both 0 hours and 3 hours after dosing and who complied with the protocol.

A total of 101 patients were enrolled in the study. One patient did not take any study medication (patient refused to participate) and was not included in any analyses. The intent-to-treat population included 100 patients, 48 in the CR oxycodone group and 52 in the CR morphine group. There were 79 patients in the pharmacokinetic-pharmacodynamic population, and 66 patients in the C_{max}/C_{min} population.

VI. RESULTS:

A. PHARMACOKINETICS:

C_{max}, C_{min}, and the scaled difference (C_{max} - C_{min}/mean C_t) are summarized in the following table. C_{min} was significantly higher in the CR oxycodone group than in the CR morphine group. The coefficient of variaton (CV) of C_{min} was 61% in the CR oxycodone group and 62% in the CR morphine group, indicating that the relative variation in C_{min} was similar with both drugs. The scaled difference was significantly lower in the CR oxycodone group than in the CR morphine group. This indicates that steady-state plasma concentrations of oxycodone showed less fluctuation than those of morphine when measured after repeated q12h dosing in the presence of stable pain control.

Mean (SE) C_{max}, C_{min}, and scaled difference (C_{max} - C_{min}/mean C_t) (C_{max}/C_{min} population)

	CR oxycodone	CR morphine
C_{max} (ng/mL)	58.1 (7.5)	47.2 (5.7)
C_{min} (ng/mL)	29.2 (3.0)*	16.0 (1.8)*
CV of C_{min} (%)	60.5	61.5
Scaled difference	0.6* (0.1)	0.9* (0.1)

*Statistically significant difference between groups, p=0.0014 for C_{min} and p=0.0041 for scaled difference

(Cross-reference: Table 9; Data Listing 9; Appendix IV)

Common opioid-related adverse experiences were treated appropriately, and only 9 of 100 patients discontinued for adverse experiences, 3 in the CR oxycodone group and 6 in the CR morphine group. Only one patient had serious adverse experiences, which were related to disease progression. This patient and one additional patient died while hospitalized during the trial. Both of these deaths were caused by disease progression, and were considered by the investigators to be unrelated to the study drug. Two additional patients were hospitalized during the trial for intercurrent diseases and conditions that were not reported as adverse experiences.

Laboratory testing was performed at the end of the trial to help explain any possible aberrant pharmacokinetic-pharmacodynamic results. Many patients had clinically significant abnormalities that were associated with the underlying disease states. No clear patterns of abnormalities that could be attributed to the study drugs were noted.

VII. CONCLUSIONS:

The peak-to-trough fluctuation in steady-state plasma drug concentrations was one-third less with CR oxycodone than with CR morphine. In addition, one-half of the variation in plasma oxycodone concentrations could be attributed to differences in oxycodone dose, while only one-tenth of the variation in plasma morphine concentrations could be attributed to differences in morphine dose. CR oxycodone provides more consistent and predictable therapeutic opioid concentrations than CR morphine. There was no difference in the relative variation in trough plasma drug concentrations with CR oxycodone compared with CR morphine.

This study did not show an association between laboratory measures of hepatic (AST/SGOT, ALT/SGPT, and bilirubin) and renal (BUN and creatinine) function and the plasma concentration profiles of oxycodone and its metabolites, noroxycodone and oxymorphone. In comparison, plasma concentrations of the active metabolite of morphine, morphine-6-glucuronide, increased with increasing BUN and creatinine levels. This provides further evidence of the consistency of plasma oxycodone concentrations in this patient population.

CR oxycodone was as effective as CR morphine in relieving pain in cancer patients. The median time to achieve stable pain control was two days with both treatments, and the number of dose adjustments required and rescue medication use were similar for both drugs. Rescue use was quite infrequent (an average of one dose per day). Pain intensity was "slight," acceptability of therapy was "good," and quality of life was similar with both treatments. The safety profiles of CR oxycodone and CR morphine were similar, and were typical of opioid analgesics. However, there were small differences that favored CR oxycodone. No patients treated with CR oxycodone experienced hallucinations, compared with two patients treated with CR morphine. Also, patients' ratings of itching and observers' ratings of scratching were lower in the CR oxycodone group than in the CR morphine group. There was a significantly more positive relationship between plasma oxycodone concentrations and analgesia compared with plasma morphine concentrations and

analgesia. However, there were no strong or predictive correlations between plasma opioid concentrations and pain intensity, MSDEQ scores, or scores for drowsiness or nausea.

While CR oxycodone was comparable with CR morphine in efficacy, there were differences in clinical pharmacokinetics that favored CR oxycodone. Similarly, the safety profiles of CR oxycodone and CR morphine were similar, but small differences suggested CR oxycodone may have benefits over CR morphine in individual patients. Overall, this study provides definitive evidence of the clinical equivalence of CR oxycodone and CR morphine in controlling cancer pain.